

**NRI: BMI Control of a Therapeutic Exoskeleton**

**NCT01948739**

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## UNIVERSITY OF TEXAS – HOUSTON MEDICAL SCHOOL PROTOCOL

### 1. **PROTOCOL TITLE:** NRI: BMI Control of a Therapeutic Exoskeleton (Brain Machine Interface Control of a Therapeutic Exoskeleton to Facilitate Personalized Robotic Rehabilitation of the Upper Limb)

Protocol Nr:

### 2. **BACKGROUND and SIGNIFICANCE**

**Relevance to robotic rehabilitation:** Stroke is the leading cause of neurological disability in the United States [1] and accounts for the poor physical health and the social dysfunction evident in survivors [32]. Hemiparesis due to stroke is the primary cause of disability [33]. Arm paresis is perceived as the primary cause of disability by individuals who have suffered stroke because of the limitations it creates in performing activities of daily living (ADL) [34]. Rehabilitation of the impaired limb is essential for improving motor function after stroke [35-36], yet only 31% of stroke survivors receive outpatient rehabilitation (CDC 2007). Therefore, effective therapy for upper-limb paresis must be addressed.

Approximately 80% of all stroke survivors suffer from upper limb paresis and only 18% of these individuals gain full motor recovery with conventional treatments in the year following stroke [2-4]. Thus, continued rehabilitation of the impaired limb is needed. Studies indicate that with proper treatment, upper extremity recovery can occur years after the stroke incident [34]. For example, repetitive, task specific training of the affected limb can result in significant motor recovery more than one year after the stroke incident [2]. Robotic devices are excellent candidates for delivering this repetitive and intensive practice. Experiments show that robot-assisted training of the impaired arm can be as effective as unassisted repeated practice of the impaired arm [37-38] and more effective than neuro-developmental therapy commonly used for motor recovery after stroke [39]. Furthermore, robotic rehabilitation systems offer increased efficiency, lower expenses, and new sensing capabilities to the therapist.

Although various aspects of robotic rehabilitation have been investigated, a significant effort has been the design of novel rehabilitation robots, including the MIT-MANUS [5] and MIME [39-40], both of which were designed for rehabilitation of the proximal upper extremity joints. Due to the success of these early systems, robotic devices for the rehabilitation of distal joints of the upper limb have also been developed, such as the MAHI Exoskeleton [28-29], RiceWrist [26], the wrist module of the MIT-MANUS [41] and wrist rehabilitation devices developed by Hesse et al. [42] and Andreasen et al [43]. Most recently, rehabilitation robots with more degrees-of-freedom (DOF) such as Rupert [6], CADEN-7 [7] and ARMin [8] that are capable of actuating shoulder, elbow and wrist joints simultaneously have also been designed.

From a mechanical design point of view, rehabilitation robots can be classified into two groups: end-effector based robots and exoskeletons. MIT- MANUS [5], a two degree-of-freedom (DOF) planar manipulator, is an example of end-effector robots. Based on an industrial 6 DOF PUMA robot, MIME [39-40] constitutes another example of end-effector based designs. Although end-effector based robots provide training capability encapsulating a large portion of the functional workspace, they do not possess the ability to apply torques to specific joints of the arm. Exoskeletons, on the other hand, are designed to resemble human

form and their structure enables individual actuation of joints. Examples of upper extremity rehabilitation exoskeletons include 5 DOF MAHI Exoskeleton [28-29], 5 DOF Rupert [6], 6 DOF ARMin [8] and 7 DOF CADEN-7 [7]. Rehabilitation engineering research has increasingly focused on quantitative evaluation of residual motor abilities in an effort to obtain an objective evaluation of rehabilitation effects [30]. Exoskeletons offer the advantage of precisely recording and monitoring isolated joint movements of the arm and wrist, and hence make a better-suited design option versus end-effector based designs for this purpose.

**Neural Interfaces as tools to achieve human-machine confluence:** The last decade has seen remarkable advances in algorithms for neural decoding and their use in assistive Brain-Machine Interface (BMI) systems to reconstitute motor function. Impressive feasibility demonstrations of non-human primates and humans controlling robotic limbs or computer cursors in real-time have been accomplished (Serruya et al. 2002; Taylor et al. 2002; Carmena et al. 2003; Wolpaw et al. 2004; Leuthardt et al. 2004; Hochberg et al. 2006, Velliste et al. 2008; Ganguly and Carmena, 2009; Bradberry et al, 2011). Current BMI systems utilize neurophysiological or metabolic signals originating in the brain to control external devices or computers. These signals are fed into a decoding algorithm that transforms them into functional outputs to control robotic limbs or screen cursors (Carmena et al, 2003; Kim et al. 2006; Hochberg et al, 2006). A closed control loop is normally established via the subject's visual feedback of the prosthetic device, although feedback from multiple modalities has been shown to enhance BMI control (Suminski et al, 2010). The neurophysiologic signals can be recorded from inside (invasive BMIs) or outside (non-invasive BMIs) the brain. Most BMIs are based on operant training of neuroelectric responses from single neuron spike trains (Fetz et al. 1969; Fetz, 2007) or scalp electroencephalogram (EEG) waves, event-related potentials and brain oscillations (for an overview see Birbaumer 2006b, Birbaumer & Cohen, 2007). Subjects or patients can learn to activate or deactivate external devices or computers based on voluntary modulation of their brain activity during motor imagery, however this training may take weeks to months and it is not clear whether these BCI systems are scalable to more than 3 independent degrees-of-freedom (McFarland et al, 2010; Bradberry et al, 2011). Based on the more recent finding that BMI training can be used for selective induction of use-dependent CNS plasticity that might facilitate motor recovery, the concept of restorative BMI has emerged (Birbaumer & Cohen, 2007, Daly & Wolpaw, 2008, Broetz et al. 2010, Caria et al. 2010, Dimyan & Cohen, 2011). Cortical control of neuroprosthetic systems is known to require adaptation in neural networks involved in motor planning and motor execution (Ganguly and Carmena, 2009; Velliste et al, 2008; Taylor et al, 2002). Although the long-term use of a BMI device has been shown to result in the formation of a stable, addressable and robust cortical map for 2D prosthetic control (Ganguly and Carmena, 2009), little is unknown about the nature of the cortical representation for BMI control of limb movements at the macro-scale of EEG.

This research aims to accelerate the development, efficacy and use of robotic rehabilitation after stroke by capitalizing on the benefits of patient intent and real-time assessment and impairment. Validation will occur using the MAHI EXO-II exoskeleton robot in a clinical setting at The Institute for Rehabilitation and Research (TIRR) in Houston, Texas. Robotic rehabilitation is an effective platform for sensorimotor training in stroke patients. A robotic device enables accurate positioning of the impaired limb while simultaneously providing assistance and resistance forces and collection of motion data that can be used to characterize

the quality of the patient's movements. First, the MAHI EXO-II, a physical human-robot interface, will be augmented with a non-invasive brain-machine interface (BMI) to actively include the patient in the control loop, thereby making the therapy 'active' and engaging patients across a broad spectrum of impairment severity in the rehabilitation tasks. This approach capitalizes on the known benefits of patient intent in movement initiation observed in other clinical studies of robotic rehabilitation and in the beneficial effects of BMI use on cortical plasticity. Second, robotic measures of motor impairment, derived from real-time data acquired from sensors on the robotic exoskeleton and from the BMI, will drive patient-specific therapy sessions adapted to the capabilities of the individual, with the MAHI EXO-II providing assistance or challenging the participant as appropriate, in order to maximize rehabilitation outcomes. Assist-as-needed paradigms in robotic rehabilitation have been shown to be efficacious; however, such paradigms are passive and driven by performance metrics that have not been sufficiently validated and verified. Additionally, intense practice and continual 'challenge' during therapy is known to improve rehabilitation outcomes.

The key contributions of this work include:

- 1) Adapting most advanced electroencephalogram (EEG) interface methods to stroke patients and developing a BMI for the control of the MAHI EXO-II that will a) increase upper limb function, b) advance understanding of brain plasticity,
- 2) Determining appropriate robotic measures of motor impairment and associated control algorithms for patient-specific therapy; and
- 3) Clinical validation in pilot studies to determine safety and efficacy of the proposed approach.

The outcomes of this study will open new horizons for addressing both empirical problems, e.g. in the interpretation of measurement data from a variety of devices and subsequently in the formation of hypotheses regarding large scale brain function (interfacing the motor, perceptual and cognitive systems) and normative problems, e.g. building health innovations for restoring upper limb function after stroke.

### **3. PURPOSE OF THE STUDY:**

The purpose of this study is to provide an alternative therapy modality where, the MAHI EXO-II, a physical human-robot interface, will be augmented with a non-invasive brain-machine interface (BMI) to actively include the patient in the control loop, thereby making the therapy 'active' and engaging patients across a broad spectrum of impairment severity in the rehabilitation tasks. Validation will occur using the MAHI EXO-II exoskeleton robot in a clinical setting at The Institute for Rehabilitation and Research (TIRR) Memorial Hermann in Houston, Texas. Robotic rehabilitation is an effective platform for sensorimotor training in persons suffering a cerebral vascular accident (stroke). A robotic device enables accurate positioning of the impaired limb while simultaneously providing assistance or resistance forces and collection of motion data that can be used to characterize the quality of the patient's movements. The aims are:

**Aim 1 (Year 1):** To augment the MAHI EXO-II, a physical human-robot interface, with a non-invasive brain-machine interface (BMI) based on the EEG to actively include the patient in the control loop, thereby making the therapy 'active' and engaging patients in the rehabilitation tasks. This user-inspired approach capitalizes on the known benefits of patient intent in movement initiation observed in other clinical studies of robotic rehabilitation and in

the beneficial effects of BMI use on cortical plasticity.

**Aim 2 (Year 2):** To develop robotic and electrophysiological (EEG-based) measures of motor impairment and recovery, derived from real-time data acquired from sensors on the robotic exoskeleton and from the BMI, that will drive patient-specific therapy sessions adapted to the capabilities of the individual, with the MAHI EXO-II providing assistance or challenging the participant as appropriate, in order to maximize rehabilitation outcomes. Assist-as-needed paradigms in robotic rehabilitation have been shown to be efficacious; however, such paradigms are passive and driven by performance metrics that have not been sufficiently validated and verified. Additionally, intense practice and continual 'challenge' during therapy is known to improve rehabilitation outcomes.

**Aim 3 (Years 3-4):** To pursue longitudinal studies using the BMI-MAHI EXO in a cohort of patients with chronic and acute stroke to study the changes in cortical plasticity (using EEG and functional magnetic resonance imaging, fMRI), motor function, and human-machine confluence as the patients learn to control the robot exoskeleton, while improving their motor performance.

#### **4. DESCRIPTION OF STUDY:**

This study is designed to develop a therapy protocol that uses robotic activities and can be used in rehabilitation of upper-extremity function after stroke. 40 adult subjects who have developed hemiparesis after stroke will participate. In addition 10 health subjects will be recruited.

First participants will go through a series of device try-out and mock therapy sessions (Aim2, year 1). We expect that each session will be two-hour-long and range from one to twelve sessions. The observation from these sessions will allow researchers to develop a therapy protocol to perform the treatment in a cohort of acute and chronic stroke subjects (Aim3, years 2-4).

**Pre-screening Procedures:** during the pre-screening process, potential subjects with stroke (acute or chronic) will be contacted by phone from a research personnel. The aim and details of the study will be explained in details and information such as demographics, medical history, medications being used, etc. will be gathered. Also subjects will be screened for MRI contraindications. The pre-screening will last about 30 minutes and will be performed in a private area.

Once this information is collected, the researcher will consult with the Dr. Francisco (PI) and he will give final approval for the subject to come to TIRR Memorial Hermann for the screening procedure.

**Screening (duration: One hour):** After subject arrives at TIRR a research personnel will meet him/her at the Motor Recovery Laboratory. The details of the study- specific procedures will be reviewed with the subject. Subject will be screened for inclusion and exclusion criteria. Signed and dated informed consent will be obtained. Demographics, medical history, and list of medications will be recorded. If the subject is female and of child-bearing age, a urine

pregnancy test will be requested before the subject undergoes MRI. A medication diary will be given to the subject and asked to document all changes in type and dosage of the medication he/she has been using throughout the study. This will allow us to differentiate a potential effect of a change in dosage or type of medication on movement recovery. After subject meets all Inclusion and Exclusion Criteria he/she will be enrolled into the study.

**Baseline Assessment (duration: two to three hours):** The baseline assessment can be on the same visit as screening and will be performed in the Motor Recovery Laboratory. Subjects will be evaluated for cognitive, psychological, upper extremity motor and sensory functions and for their independence in daily living activities. Patients will also undergo one-hour MRI scan.

The tests are:

**I- Baseline neurologic and functional status:**

In addition to abstracting basic demographic (e.g., age, sex, race/ethnicity) and clinical information (e.g., type and location of stroke) from the medical record, the following measures will be recorded before treatment by the evaluator:

- a) NIH Stroke Scale: The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. A score of 0 indicates normal function, while higher score is indicative of some level of impairment.
- b) Manual Muscle Testing (MMT): The manual muscle testing will help to differentiate subjects with residual limb function. A score of 2 (-) in MMT, or the ability to move the limb segment with gravity eliminated, is required for elbow and wrist flexor and extensor muscle groups.
- c) Handedness: the dominance of right or left hand in daily activities will be measured with Edinburgh Handedness Inventory. Subjects will be questioned which hand they prefer to use for example to write, to draw to throw a ball, etc. (Oldfield R.C, 1971)
- d) Cognitive Functions: Folstein Mini Mental State Examination (MMSE) provides information about orientation, attention, learning, calculation, delayed recall, and construction. Several studies report acceptable validity of MMSE as a screening instrument and its relationship to functional outcome in stroke patients (Tombaugh et al. 1992; Agrell B, et al. 2000; Zwecker M, et al. 2002; Appelros et al,2005).
- e) Unilateral Spatial Neglect: Letter Cancellation Test is used to evaluate the presence and severity of visual scanning deficits, and is used to evaluate unilateral spatial neglect (USN) in the near extrapersonal space(Diller et al,1974)
- f) Sensory functions: The joint position sense of proprioception will be used to sense participant's ability to perceive the position of wrist joint, and be measured with vision occluded and minimal exteroceptive cues. Results will be documented as normal, impaired or absent (ref?).
- g) Psychological functions: Hamilton depression scale (HAM-D scale, Hamilton, 1960) will be used to determine patient's level of depression. The HAM-D form lists 21 items, however the scoring is based on the first 17 items. Eight items are scored on a 5-point scale, ranging from 0=not present to 4=severe; nine are scored from 0-2.



## II- Conventional Clinical Motor Tests

The motor tests will be used to measure therapeutic improvement. The tests were selected to sample functional arm and hand movements, and have been shown to be sensitive to rehabilitation and demonstrated reliability. The tests will be administered by the outcome evaluator. The motor tests are:

- a) Fugl-Meyer Arm Motor Score: Is a stroke-specific, performance based impairment index. It quantitatively measures impairment, based on Twitchell and Brunnstrom's concept of sequential stages of motor return in hemiplegic stroke patients (Fugl-Meyer 1975). It uses an ordinal scale for scoring of 32 items for the upper limb component of the F-M scale; (0: cannot perform; 1: can perform partially; 2: can perform fully). Excellent interrater and intrarater reliability and construct validity have been demonstrated, and preliminary evidence suggests that the Fugl-Meyer assessment is responsive to change.
- b) Jebsen-Taylor Hand Function Test: (Jebsen et al., 1969): This motor performance test measures the time needed to perform 6 everyday activities (e.g., flipping cards, feeding) using both upper extremities. Administration of JTHFT subtests will be discontinued after 180 sec if the participant cannot complete the task by that time. The total JTHFT score is the sum of task completion times, with lower times representing better performance (Jebsen et al 1969).
- c) Action Research Arm Test: will be performed to assess subjects' ability to manipulate objects differing in size, weight and shape on a horizontal and vertical plane (Lyle, 1981)
- d) Grip Strength: A dynamometer measures maximum gross grasp (kg) averaged over attempts with each hand. The minimum possible value of zero kg will be assigned when the participant cannot actively flex the fingers or grasp the dynamometer (Mathiowetz et al 1985).
- e) Pinch strength: A pinch gauge measures maximum pinch force (kg) averaged over attempts with each hand. The minimum possible value of zero kg will be assigned when the participant cannot actively squeeze the pinch meter between thumb and index finger. Pinch dynamometry appears to be useful to measure improvement in grip strength after hand-surgery in persons with tetraplegia (Vanden Berghe et al 1991).

## III- Robotic Surveys:

- a) Pain and Fatigue: will be measured on a visual analogue scale. After each training session, participants will be asked to rate their current pain and fatigue on an 11-point scale ranging from (0 = none to 10 = worst possible) (New et al 1997 )
- b) Subject and Therapist Survey of Robotic Training: Subjects will be questioned after each session to rate their fatigue, discomfort, motivation, etc. level on a 4 point ordinal scale (0= strongly disagree, 4= strongly agree). Therapist will rate their perception on ease of set up, ease of use on a 4 point ordinal scale (0= strongly disagree, 4= strongly agree).
- c) System Usability Scale (SUS): Subjects will be questioned to understand their response to the BMI robotic training system by responding to questions on the SUS.

## IV- Robotic motor coordination measures:

Robotic measures will be calculated by post-processing the data acquired before, after and during treatment sessions.

- a) trajectory error (TE) measure: is defined as a normalized difference between the desired and the participant's trajectory from one point in the workspace to another.
- b) smoothness of movement (SM) measure: is a correlation coefficient that express the correlation between the participant's speed profile and a speed profile utilizing the minimum jerk principle. It takes values between 0-1, where 1 indicates perfect correlation with the optimally smooth speed profile and 0 indicating no correlation. Both TE and SM demonstrated strong correlation between clinical measures of arm function, such as Fugl-Meyer and Action research Arm test (Celik et al, 2010)

#### **V- Electrophysiological testing:**

Electroencephalogram (EEG): The EEG test is performed to measure the electrical activity in the brain and to examine the cortical dynamics. It also allows for better understanding of the effects of electrical activity generated in different areas of the brain. EEG only measures brain activity and does not induce electrical current in the brain. It is non invasive and has been used extensively in clinical practice for diagnosis or neurological conditions such as epilepsy. There are no risks associated with EEG other than a mild discomfort caused by the tightness of the net. The investigator will adjust the net to allow for the comfort of the subject.

#### **VI- Neuroimaging: MRI (structural & functional);**

The structural and functional MRI is performed to understand the reorganization of cortical areas associated with motor recovery. Morphological changes (structural plasticity) will be measured with structural MRI, and reorganization of neural activity (functional plasticity) will be measured with the functional MRI. MRI is noninvasive and has been used extensively in clinical studies. In order to eliminate the risks associated with magnetic field, subjects will be scanned for MRI safety.

The clinical and behavioral tests will be administered by trained research personnel.

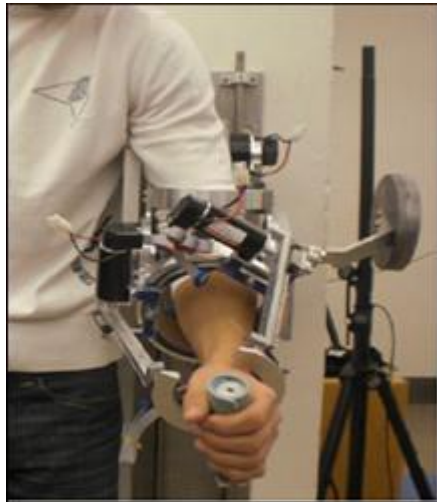
**Intervention Period (duration: two- hours per visit).** The intervention part consists of two phases:

- a) Simulated therapy sessions
- b) Real therapy sessions

##### **a) Simulated therapy sessions (duration: two- hours per visit, up to twelve visits):**

First healthy and stroke affected subjects will be familiarized to control the InMotion Robot Manipuladum device with their thoughts. This calibration and familiarization with robotic training, may take over several sessions. During this period subjects will begin training to learn how to use their intentions to move the exoskeleton through repeated single joint and multi-joint movements while they wear the BMI system. During BMI training, healthy subjects/patients will essentially imagine moving their limb (muscle activity from the limbs will be monitored via electromyography, EMG, to ensure that only 'movement thoughts' are





**Figure 2. MAHI Exo-II robotic device**

used to control the robot) while watching the robot's resulting movement outputs (patients will be asked to actively attempt to perform the movements). Later, subjects will start using the exoskeleton device (Rice Wrist, MAHI Exo-II). During the training sessions the single joint and/or multi-joint targeted movements will be self-selected and self-initiated by the subject. The aim is to have them use the BMI and exploit the robot's capacity to increase the range of paretic arm movement by getting the robot to move up and down through a larger range than they can produce on their own (i.e., evoking robotic assistance). For each group this is accomplished by using the decoder's outputs to control the exoskeleton (Figure 2) by closing the loop via real time visual feedback of the robot's movement, that is, the reconstructed trajectories of the elbow and wrist joints decoded from EEG will be utilized to control the exoskeleton in real-time. The robot will operate in an "assist-as-needed" mode. Then after a rest period the subjects will sit passively while the robot replays the recorded movements, again with concurrent EEG recordings.

We expect that each test session will be two-hour-long. These sessions will be repeated until subject gains confidence in using the robot arm. After a washout period of minimum 1-week from the last try-out session (if subject has participated in try-out sessions) subjects will participate in robotic training of arm movements 3 times/week for 4 weeks. Activities will be performed with the affected arm only.

The tasks will be repeated multiple times per session for improved performance. Graphic feedback about performance will be given after each attempt in order to maintain motivation. Rest breaks will be given in order to avoid fatigue. At the end of each therapy session adverse events will be collected and the subject will be asked to rate his/her level of fatigue, pain, and satisfaction with the activities during the session. The staff member will record the time needed for equipment set-up, the ease of instructing the patient in the activity, and the potential therapeutic value of the activity.

If possible data acquired before-and-after, and during the therapy sessions will be analyzed offline. If needed the existing protocol of 3x/week for 4 weeks will be modified and improved so that a final protocol is created and used in the second phase of the intervention period, i.e., active therapy sessions, in a cohort of subacute and chronic stroke subjects (Aim3, years 3-4).

b) Real therapy sessions (duration: two- hours per visit, twelve visits).

During this phase the therapy sessions will be supervised by a research personnel, who will set up the EMG, EEG, robotic device, instruct the subject and supervise the activity. During each session subject will be sitting on a comfortable chair and affected arm will be placed inside the padded exoskeleton the MAHI EXO-II. The real therapy sessions will be about two-hours long

and will be repeated three-times per week, over four-week training.

The robotic training is investigational. The outcome measures of motor function have been used in clinical research but are also relevant to evaluate progress in clinical practice.

**Post-treatment and Follow-Up Assessment (duration: two to three hours):** During this period subjects will be asked to come within a-week after they have completed the study, at week-2 and at month-2. Motor functions tests and robotic measures and MRI scan will be repeated.

**Videotape/ Photography:**

Portion of assessment sessions will be videotaped and/or photographed. Subjects will be asked to move or manipulate some objects with the arm while a project staff member will record or photograph. Subjects' consent will be required to perform and photography or videotaping. Screening, assessment and treatment sessions will be held at The Institute for Rehabilitation and Research and neuroimaging (MRI) will be performed at The Methodist Hospital or MRI imaging center at UTHealth Medical School. Calibration sessions will be held in part at University of Houston. Approximately 22 visits over a 6-months period will be required. Schedule of assessments is shown in Table 1.

Table 1. Schedule of visits

Assessment	Screening	Baseline Assessment	Intervention period												Post-treatment Assessment	Follow-Up Assessment at 2weeks	Follow-Up Assessment at 2 months
	Day7- to Day1	Day 1	Day 4(±3) to Day 15(±3)												Day 19(±3)	Day 33 (±3)	Day 79 (±5)
	Visit 1	Visit 2	Visit 3-12												Visit 15	Visit 16	Visit 17
ICF	X																
I/E Criteria	X	X															
Demographics	X	X															
Medical History	X	X															
NIH Stroke Scale		X												X	X	X	
Manual Muscle Testing (MMT)		X															
Handedness		X															
Mini Mental State Exam (MMSE)		X															
Neglect- Letter Cancellation test		X															
Proprioception- Joint sense		X															
Depression		X															
Fugl-Meyer		X															
Ashworth Scale		X												X	X	X	
Grip Strength		X												X	X	X	
Pinch Strength		X												X	X	X	
JTHFT		X												X	X	X	
ARAT		X												X	X	X	
Robotic Measures		X												X	X	X	
Electroencephalography (EEG)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MRI contraindications	X																
MRI Scan structural		X												X			
MRI Scan		X												X			

functional																	
BMI controlled Robotic training			X	X	X	X	X	X	X	X	X	X					
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X		X		X

***Specimens to be collected, including frequency and size/amount:*** None.

## 5. SUBJECT POPULATION:

We assume to screen 60 adults with hemiparesis caused by stroke and enroll 30 of the screen participants over the course of the project from the TIRR Memorial Hermann outpatient clinic and from the Houston area. In order to reach the goal of „30 participants enrollment“, we expect to screen 60 subjects with stroke. In addition 20 healthy subjects will be recruited in order to meet the goal of 10 healthy subjects“ enrollment.

### Inclusion and Exclusion Criteria for Subjects with Stroke:

#### Inclusion Criteria:

Subject will be included if they have;

1. Diagnosis of unilateral cortical and subcortical stroke confirmed by brain CT or MRI scan;
2. Subacute or chronic stroke; interval of at least 3month and interval of at least 6 months from stroke to time of enrollment, respectively;
3. No previous clinically defined stroke;
4. Age between 18-75 years;
5. Upper-extremity hemiparesis associated with stroke (manual muscle testing score of at least 2, but no more than 4/5 in the elbow and wrist flexors);
6. No joint contracture or severe spasticity in the affected upper extremity: i.e., significant increase in muscle tone against passive ROM is no more than ½ of full range for given joint e.g., elbow, wrist and forearm movements.
7. Sitting balance sufficient to participate with robotic activities;
8. No neglect that would preclude participation in the therapy protocol;
9. Upper limb proprioception present ( as tested by joint position sense of wrist);
10. No history of neurolytic procedure to the affected limb in the past four months and no planned alteration in upper-extremity therapy or medication for muscle tone during the course of the study;
11. No medical or surgical condition that will preclude participation in an occupational therapy program, that includes among others, strengthening, motor control and functional re-training of the upper limbs;
12. No contraindication to MRI;
13. No condition (e.g., severe arthritis, central pain) that would interfere with valid administration of the motor function tests;
14. English-language comprehension and cognitive ability sufficient to give informed consent and to cooperate with the intervention.

#### Exclusion Criteria:

1. Orthopedic limitations of either upper extremity that would affect performance on the study;
2. Untreated depression that may affect motivation to participate in the study;

3. Subjects who cannot provide self-transportation to the study location.

Handling situation in case of a possible mood disorder:

If subject's score in the depression scale suggest the possibility of a mood disorder, research team member will inform Dr.Francisco directly, so he can investigate it further and discuss options with the subject, including seeing a UTHealth psychiatrist, Dr.Dhamendra Kumar, who has a clinic at TIRR Memorial Hermann 2-3 times a week. Dr.Francisco will briefly document as a report in subject's research file.

Inclusion and Exclusion Criteria for Health Subjects:

Inclusion criteria:

- able to understand and sign the consent form
- age 18-65

Exclusion criteria:

- Previous history of or MRI findings consistent with brain tumors, strokes, trauma or arterial venous malformations
- Contraindication to MRI
- Pregnancy

**6. SUBJECT ENROLLMENT:**

Potential subjects will be identified by the following sources:

1. Flyers will be posted in the TIRR Memorial Hermann outpatient clinic and TIRR Memorial Herman Adult and Pediatric Outpatient Rehabilitation. Attending physicians and therapists may refer their stroke outpatients to the study.
2. Study will be advertised to general public through newspapers and radio programs.

After subjects are identified by their treating physicians or therapists, they will be contacted by phone or e-mail. Alternatively they can contact study coordinator to request more information about the study. During a phone call, a brief pre-screening procedure will be applied. Demographics and medical information such as psychiatric, drug and alcohol history as inclusion and exclusion criteria will be gathered. Dr. Francisco will review the information gathered during phone screening and will agree or decline subject's enrollment into the study. Potential subjects will be invited to come for a screening visit to the UTHealth Motor Recovery Laboratory at TIRR Memorial Hermann. Any information gathered during phone screening will be stored in a locked file cabinet and password protected electronic file.

During the screening visit, informed consent will be obtained by an investigator at TIRR. The subject will meet with the PI and the co-investigator. The test procedures will be described and the testing equipment will be shown to the subject. A co-investigator will clearly explain all the procedures and risks of the testing outlined in the consent form. The subject will be given

an hour to consider their decision and will be encouraged to ask questions, both during the initial interview and throughout the study. The PI or a co-investigator will answer any questions regarding the study at the time consent is given. Once enrolled, the subject may pause or terminate his/her participation at any time during the study.

## **7. DATA ANALYSIS:**

Data analysis: Analyses will be performed with two-tailed significance tests at the 95% confidence level and are planned using parametric methods with continuous variables. Repeated measures ANOVAs with repeated measures on test-day (Day 1 to Day13) will be used to determine the effects for the EEG, robotic and clinical measures. This allows determination of the effects of BMI training on the given variables across test days. A Kenward Rogers adjusted degrees of freedom will be used due to the relatively small sample size. Power analysis from our preliminary studies (PI Boake, Co-I O'Malley) indicates that, according to the improvements on FM, ARAT and JT measures, the current subject number will give us more than 90% of estimated power. We will compare clinical and robotic measures of motor impairment for each pair (FM-TE, FM-SM, ARAT-TE, ARAT-SM, JT-TE, and JT-SM) across all participants. We will use regression analyses to investigate the correlation between clinical, EEG and robotic measures at different days of treatment. The data are collected at the same stage of treatment for all participants to negate treatment effects. Regression analyses will be carried out using the 24 paired data sets, with the analysis providing the correlation coefficient  $r$  (Person's  $r$ ) and  $p$  value that represents the significance of the slope of the linear fit. A significant slope assures that the correlation coefficient  $r$  is also significant, i.e. there is a significant correlation between the variables.

Analysis for neuroimaging scans: To assess structural changes, high-resolution anatomical images of the entire brain (using a 3 dimensional fast field echo sequence in axial orientation parallel to the line formed by the anterior and posterior commissures (AC, PC) will be acquired (in-plane resolution approx. 1 mm, slice thickness approx. 1mm, total acquisition time in the order of 10 min, parallel imaging options will be avoided to obtain high signal to noise ratios and good gray-white matter contrast). Images will be analyzed using the Freesurfer software ([surfer.nmr.mgh.harvard.edu](http://surfer.nmr.mgh.harvard.edu)), which allows the segmentation and quantification of white/gray matter changes and the quantification of their volume. Changes in volumes of brain structures accessible to Freesurfer (cortical and subcortical structures) will be quantified during the course of the study.

Diffusion tensor images (DTI), that is, spin-echo echo-planar images oriented in the same fashion as the anatomical images (parallel to the AC-PC line, in-plane resolution approx. 1.8 mm, slice thickness approx. 3 mm, number of diffusion-weighted directions: approx. 25 with an estimated acquisition time in the order of 10 min) will be acquired to assess changes in the white matter fiber structure of the brain during the study. DTI images will be analyzed using the trackvis software ([www.trackvis.org](http://www.trackvis.org)) by segmenting the pyramidal tracts and quantifying changes in fractional anisotropy (FA, a measure of tract integrity) during the course of the study.

To assess motor function, fMRI image data will be acquired consisting of echo-planar images oriented in the same fashion as the high-resolution anatomical images (parallel to the AC - PC line). The fMRI paradigm will consist of visual and/or auditory stimuli activating the motor

cortex and will last about 10 - 15 min. Activation will be quantified by making use of the BOLD effect, thereby identifying and quantifying activation strength and extent of activated brain areas. AFNI ([afni.nimh.nih.gov/afni](http://afni.nimh.nih.gov/afni)) and FSL ([www.fmrib.ox.ac.uk/fsl/](http://www.fmrib.ox.ac.uk/fsl/)) software packages will be used for the analysis.

In addition to goal-directed fMRI images, also fMRI images will be acquired during which the subject is passively lying in the scanner with their eyes open (approx. 5min). These resting state images will be utilized to identify the extent of several networks in the brain, such as the motor network and the resting state network. Changes in the motor network may also be indicative of brain plasticity. Brain networks will be identified using the AFNI correlation analysis software.

MRI is noninvasive and has been used extensively in clinical studies. In order to eliminate the risks associated with magnetic field, subjects will undergo the standard procedure for identifying potential contra-indications for MRI (at TMH, these consist of a standard questionnaire and a subsequent interview with a qualified MR expert).

Cortical activity assessment with electroencephalogram (EEG): EEG activity will be assessed in all participants using standardized procedures during baseline assessment and at least a week before the first treatment session, and after the last treatment session. EEG will be sampled with 64 electrodes using an electrode cap, which places the electrodes in the standard 10-20 international placement system (Electro-Cap International, Inc). Ground electrode is built into the cap and will be at site AFZ.

*Decoding of motor intent from scalp EEG* - Neural decoders can be designed to predict state estimates as a discrete classification of multiple internal states such as intended spatial targets to move top or down or left or right (see Fig. 7 for an example of an experimental protocol involving center-out reaching movements to 3D spatial targets), or predictions of continuous time variables of endpoint hand trajectories or angular kinematics that could serve as reference signals to an upper or lower limb prosthetic device, powered exoskeleton or to control computer cursors, spelling devices or virtual keyboards. In this regard, we have demonstrated the feasibility of designing BEG-based neural interfaces to infer upper and lower limb movements from scalp EEG [34],[53-54]. Recently, we used a multivariate decoding approach grounded on machine learning methods that maximize the prediction accuracy of hand kinematics from a plurality of scalp EEG electrodes. Cortical potentials and finger joint angles were simultaneously recorded from five healthy human subjects while they naturally reached for and grasped any one of five objects (calculator, CD, espresso cup, zipper and a beer mug) in front of them. Offline, we reconstructed the hand kinematics from EEG activity and compared it with the measured kinematics, with the decoding accuracy expressed as the correlation coefficient ( $r$ ) between the two. To translate cortical activity into grasping kinematics, we extracted the fluctuations in the amplitude of slow cortical potentials filtered in the low delta band (0.1-1.0 Hz) [34], and used a genetic algorithm (GA) to optimize the feature space of a linear Wiener filter decoder with respect to decoding accuracy (i.e., the fitness function for the GA). Next, we decoded the temporal evolution of synergies as subjects reached for and grasped the objects. Synergies were calculated as principal components (PCs) of the finger movement [78].



Within subject comparison of after treatment vs. baseline will be performed, using paired t-test. Subjects' ratings of pain and fatigue after each therapy session will be compared the pain and fatigue ratings, to determine if there was unacceptable to subjects. The level of significance used will be  $p < 0.05$ .

## **8. POTENTIAL RISKS/DISCOMFORTS:**

### **Electroencephalography (EEG):**

The EEG test is performed to measure the electrical activity in the brain and to examine the dynamic changes. It also allows for better understanding of the effects of electrical activity generated in different areas of the brain. EEG only measures brain activity and does not induce electrical current in the brain. It is non-invasive and has been used extensively in clinical practice for diagnosis or neurological conditions such as epilepsy. There are no risks associated with EEG other than a mild discomfort caused by the tightness of the net or some discomfort and skin irritation. The investigator will adjust the net to allow for the comfort of the subject.

**Electromyography (EMG):** The EMG, involves testing of the muscle activity thorough electrical signals. In the current project, it will allow to ensure that only „movement thoughts“ (imagery movement) are used to control the robot. It is non-invasive and non-painful to the subject and has been used widely in clinical or research settings. The risks associated with surface EMG is some skin irritation.

### **Magnetic Resonance Imaging (MRI):**

The structural MRI is performed to measure the structural connectivity of the corticospinal tract and the functional MRI is performed to measure signal changes in the cerebral cortex. MRI is noninvasive and has been used extensively in clinical studies. In order to eliminate the risks associated with magnetic field, subjects will be screened for MRI contraindication. All scanning sessions will be supervised by a research member.

### **Robot-assisted training:**

Patients with spinal cord injury sometimes develop pain or discomfort in the shoulders and arm. In an ongoing study in our laboratory with subjects who are undergoing robotic training for three- hours per session and three-sessions per week for four weeks, didn't show any significant fatigue, discomfort or pain lasting longer than 24 hours after training (Yozbatiran et al, 2012). If there is evidence that pain or fatigue is worsened by the therapy, the sessions will be reduced or discontinued. All therapy sessions will be supervised by a project staff member. The robotic device has a safety shut-off mechanism that can be activated by the supervising staff member in order to immediately eliminate any mechanical force applied to the subject.

### **Assessment/Questionnaires:**

All assessments will be performed in a designated room inside Motor Recovery Laboratory. None of these tests are either painful or uncomfortable to perform. In order to prevent potential embarrassment during the testing the test will be done individually and in private. If subjects feel uncomfortable in answering any of the questions they may stop the study at any time.

**Monitoring plan for safety of subjects:**

In order to ensure subjects safety researchers will take following measures;

- 1- Visits: All visits will be performed in an isolated room to protect participant's privacy.
- 2- Training sessions: Dr.Yozbatiran is a physical therapist and a research member. She will be present during all training sessions and closely monitor subject for excessive fatigue, pain or discomfort. If any of these conditions occur, she will adjust the protocol to the functional level of subject by giving more frequent and longer rest breaks. If the problem persist for 24 hours at the same level of pain and/or fatigue or increases the symptoms will be reported as adverse event.
- 3- Any adverse event, significant or non-significant will be reported to IRB by following IRB reporting guidelines. An adverse event log will be used.
- 4- All personal information will be de-identified and saved in locked cabinets and password controlled computers and password controlled databases.

**9. POTENTIAL BENEFITS:**

As with any study focusing on basic research, the subjects will derive no direct benefit. The results of these studies may benefit subsequent future subjects if BMI control of a therapeutic exoskeleton proves to be effective. We envision that in the near future the information obtained from the proposed research will provide a better understanding for treatment options of upper extremity motor function in adults with stroke. The benefits of participating in this study may be improved arm and hand movement. However, there may be no benefit from participating in this study.

**10. RISK-BENEFIT RATIO:**

The clinical tests used in this study are widely used and are virtually risk free. There is some risk of fatigue, boredom or impatience, which will be counteracted by giving subjects sufficient breaks at specific time intervals and more breaks upon request. The robot devices are designed with hardware and software safety features that minimize the risk of injury due to the use of the robot. A series of automatic motion stop features are implemented to limit movement to a set of safe boundaries. The exoskeleton cannot move outside of the normal range of motion of the individual user. There is some risk of minor injury due to rubbing while using the robot. There is also a risk of pressure sores where the exoskeleton is attached to the user. A therapist will be present to apply padding to the robot where/when necessary to prevent rubbing.

As with any research study, loss of confidentiality is a possible risk, although we will take every precaution to protect the subjects' privacy, including using identification codes on all forms, with only a single master key relating the identification codes to the subjects' identifying information, which will be kept in a locked cabinet at TMH, UT and UH. We will take every precaution to protect the subjects' privacy, including using identification codes on all forms, with only a single master key relating the identification codes to the subjects' identifying information, which will be kept in a locked cabinet. Scalp EEG is a non-invasive technique that does not present risks to the subject. The EEG procedures are widely used in

research and are not known to be physically harmful to human subjects. There is a possibility that participants will become bored, tired or distressed during the experimental session due to the wearing of the EEG cap. Steps will be taken to avoid this and to address it promptly should it occur. Breaks will be taken if the participant becomes tired or distressed. Participants are free to call a break or end the experimental session whenever they see fit without penalty. Given the amount of information about brain dynamics and motor control to be learned from stroke patients, and the potential improvement of arm and hand movement in these patients, it is believed that these benefits outweigh the risks mentioned above.

## **11. CONSENT PROCEDURES:**

Informed consent will be obtained from the subject at Motor Recovery Laboratory at The Institute for Rehabilitation and Research. After the patient is confirmed by Dr. Francisco (PI) as meeting study criteria and he/she is interested in participating, informed, written consent will be obtained by the study coordinator.

In addition a photography/videotaping consent will be obtained from the subject, if he/she agrees to be photographed / videotaped during the assessments or treatment sessions.

## **12. CONFIDENTIALITY PROCEDURE:**

All data will be coded with identification number. The database will be in a password – protected computer and kept in a locked file cabinet.

## **13. COSTS**

The subject will not be expected to pay any costs.

## **14. PAYMENTS:**

Subjects who travel to the study appointments will be reimbursed \$20 per screening, assessment and treatment visit in order to pay for parking and travel.

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